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METHODS

Regional Myocardial Metabolism in Patients With Acute Myocardial Infarction Assessed By Positron Emission Tomography

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Positron emission tomography has been shown to distinguish between reversible and irreversible ischemic tissue injury. Using this technique, 13 patients with acute myocardial infarction were studied within 72 hours of onset of symptoms to evaluate regional blood flow and glucose metabolism with nitrogen (N)-13 ammonia and fluorine (F)-18 deoxyglucose, respectively. Serial noninvasive assessment of wall motion was performed to determine the prognostic value of metabolic indexes for functional tissue recovery. Segmental blood flow and glucose utilization were evaluated using a circumferential profile technique and compared with previously established semiquantitative criteria.

Relative N-13 ammonia uptake was depressed in 32 left ventricular segments. Sixteen segments demonstrated a concordant decrease in flow and glucose metabolism. Regional function did not change over time in these segments. In contrast, 16 other segments with reduced blood flow revealed maintained F-18 deoxyglucose uptake consistent with remaining viable tissue. The average wall motion score improved significantly in these segments ($p < 0.01$), yet the degree of recovery varied considerably among patients. Coronary anatomy was defined in 9 of 13 patients: patent infarct vessels supplied 8 of 10 segments with F-18 deoxyglucose uptake, while 10 of 13 segments in the territory of an occluded vessel showed concordant decreases in flow and metabolism ($p < 0.01$).

Thus, positron emission tomography reveals a high incidence of residual tissue viability in ventricular segments with reduced flow and impaired function during the subacute phase of myocardial infarction. Absence of residual tissue metabolism is associated with irreversible injury, while preservation of metabolic activity identifies segments with a variable outcome. Positron emission tomography may allow early identification of viable but jeopardized tissue and provide guidelines for aggressive therapy to salvage endangered myocardium.

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Evolving myocardial infarction is a complex pathophysiologic process that is affected by changes in residual blood flow and energy demands. For example, the high incidence of coronary thrombosis observed on arteriography early after the onset of symptoms (1,2) implicates acute thrombotic coronary occlusion as the initial event in many patients. However, thrombotic occlusion is noted less frequently when angiography is performed later in the clinical course (3). This suggests spontaneous recanalization and reperfusion in a considerable number of patients. Resultant interpatient variation in the degree of residual blood flow is further modified by possible collateral blood flow (4). On the other hand, the energy demand may also change during the evolution of the myocardial infarction because of alterations in work load or because of therapeutic interventions and it therefore contributes further to the interpatient variation (5).

Thus, estimation of extent and "completeness" of myocardial necrosis from the time elapsed since the onset of symptoms is difficult in any given patient (6). Clinical studies (7) reveal variable changes in regional myocardial func-

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tion during the first 24 hours of infarction and suggest that myocardial infarction may not be completed within a few hours. Recurrent chest pain, repetitive rises in serum cardiac enzyme levels and infarct extension by electrocardiography often occur during the first few days of infarction. Also, histopathologic studies (8) in dying patients during the acute phase of a myocardial infarction reveal large variations in the extent of necrosis relative to the occluded vascular bed.

These clinical and histologic data suggest that an admixture of necrotic and ischemic but viable myocytes may persist for some time after the onset of symptoms. Moreover, the relative distribution of both cell types may change over time. The clinically important task is detection of "incomplete infarction" in order to salvage myocardium at risk (6). Evaluation of blood flow and function alone is limited in distinguishing viable but "stunned" from necrotic myocardium (9). Electrocardiographic Q waves are not specific for transmural necrosis and symptoms may not be present despite ongoing ischemia.

Previous animal experiments (10,11) have demonstrated that metabolic imaging with positron emission tomography can differentiate reversible from irreversible tissue injury after transient ischemia. Reversible tissue injury characteristically revealed enhanced glucose utilization relative to blood flow, whereas blood flow and glucose utilization were decreased concordantly in irreversible tissue injury. The purpose of this study was therefore twofold: a) to utilize positron emission tomography for evaluating regional myocardial glucose metabolism in patients with acute myocardial infarction in order to define extent and degree of infarction, and b) to correlate regional metabolic findings with the outcome of regional function.

Methods

Study patients. The study group consisted of 13 patients (9 male and 4 female) admitted to the coronary care unit with the diagnosis of acute myocardial infarction by electrocardiographic or serum enzyme criteria, or both. All patients were studied within 72 hours of the onset of acute symptoms. Patients in cardiogenic shock or on artifical ventilation or patients with complex arrhythmias were excluded. The mean age was 65 years (range 42 to 83). Ten patients showed anterior, one inferior and one posteroinferior infarction on electrocardiogram; the infarct site was undetermined in one patient with left bundle branch block. Twelve patients developed Q waves in the leads reflecting the acute infarction. Two patients had electrocardiographic evidence of a previous inferior infarction.

Peak serum levels for creatine kinase (CK) averaged 1,384 ± 1,640 U/liter (normal 20 to 120 U/liter and for CK-MB isoenzymes 39.9 U/liter (range 9 to 179, normal <4). Eight patients underwent coronary arteriography before hospital discharge. Autopsy was performed in one patient who died 11 days after the onset of symptoms.

The study protocol and consent form were approved by the UCLA Human Subject Protection Committee. Each subject was informed about the investigative nature, purpose and possible risks of the study before written consent was obtained.

Positron emission tomography. *Image acquisition.* Tomographic imaging was performed with an ECAT II tomograph (CTI). Regional myocardial blood flow was assessed with nitrogen (N)-13 ammonia and exogenous glucose utilization with fluorine (F)-18 2-deoxyglucose (12). All patients fasted overnight in order to standardize the dietary state. After transmission images were recorded to enable correction for photon attenuation, four to six contiguous cross-sectional images (1.0 to 1.5 cm apart) of relative myocardial blood flow were obtained after intravenous administration of N-13 ammonia (15 to 20 mCi). F-18 deoxyglucose (10 mCi) was then injected intravenously, a 40 minute period allowed for myocardial F-18 deoxyglucose uptake, and cross-sectional imaging was performed at levels corresponding to those obtained with N-13 ammonia. Patient positioning for each image set was aided by marking the subject's chest with a felt pen and aligning the marks with the reference laser light beam of the tomograph. The total study time averaged about 2.5 hours. Both radionuclide injections resulted in a whole body radiation of less than 400 mrad per patient. Before injection of F-18 deoxyglucose, venous blood was withdrawn for determination of plasma concentrations of glucose, lactate and free fatty acid to detect possible differences in plasma substrate levels between individual patients.

Image analysis. The cross-sectional images were analyzed with an operator-interactive computer program using circumferential profile techniques (12). The program normalizes the recovered F-18 and N-13 counts within each myocardial cross section to maximal activity over the entire left ventricle and displays them slice by slice as a function of the angle around the center of the left ventricle. Segmental activity is then expressed as percent of maximal myocardial activity. Because of the partial volume effect, count recovery varies for each tomographic plane and along the myocardial cross-sectional image of the left ventricle. Thus, observed count data are compared with normal values for 12 sectors (each 30°) in each tomographic plane established previously in normal volunteers (12). Regional reductions in N-13 ammonia uptake below 2 SD of the normal mean in the corresponding segment identify myocardial segments with reduced blood flow (Fig. 1 and 2). Persistence or absence of metabolic activity in these segments is then defined by regional F-18 deoxyglucose uptake. Normal myocardium is characterized by a close match of flow and glucose utilization because both are regulated by regional myocardial energy demand. The same is true for scar tissue with low flow and substrate requirements.

On the basis of these theoretical considerations and experimental evidence (13), "PET infarction" was defined as

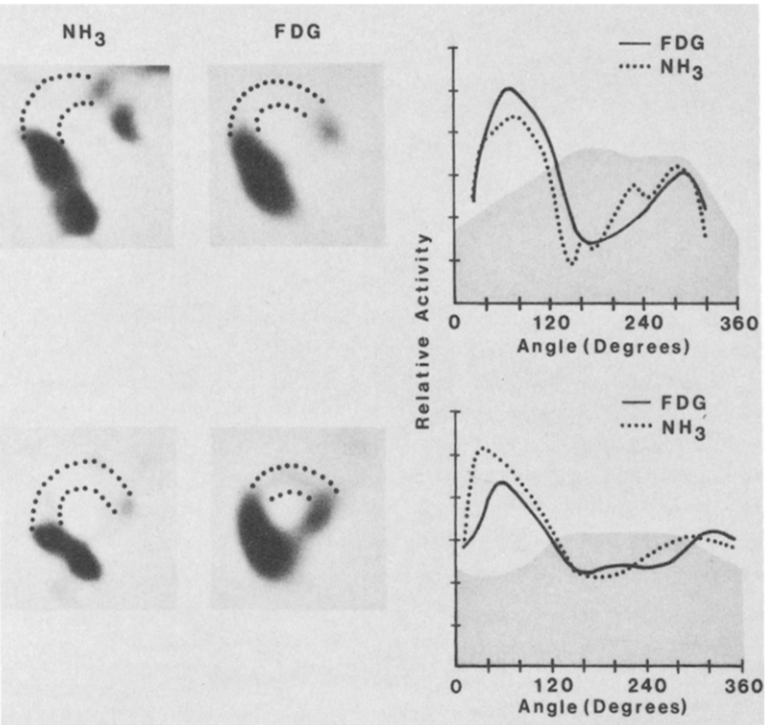


Figure 1. Patient 13. Cross-sectional images obtained after administration of N-13 ammonia (NH_3) and F-18 deoxyglucose (FDG) 42 hours after the onset of symptoms. Two planes through the mid- and distal left ventricle are displayed. Uptake of both N-13 ammonia and F-18 deoxyglucose is decreased in the anteroseptal segments of the left ventricle (matching defect) (deliniated by **dotted lines**). The respective circumferential profiles displayed on the **right** for N-13 and F-18 activity distribution show concordantly decreased activity in the anteroseptal segments (160 to 300°) fulfilling criteria of infarction (''PET infarction''). The **shaded areas** represent values of more than 2 SD below the mean values of a normal population (12).

concordant segmental reduction of recovered N-13 and F-18 counts of at least 2 SD below normal in two or more contiguous sectors (12). In viable but compromised myocardium, blood flow is decreased but metabolic activity is maintained resulting in disproportionate regional uptake of F-18 deoxyglucose in comparison with flow. Consequently, ''PET viability'' was defined as the F-18/N-13 count difference greater than 2 SD above normal in two or more contiguous sectors (12). For comparison of regional myocardial N-13 and F-18 counts with regional function, the left ventricle was divided into five large segments: an anterior, septal, apical, lateral and inferoposterior segment (12).

Assessment of segmental function. Regional function was determined on the day of the tomographic study and again 6.0 ± 4.6 (SD) (range 1.4 to 12) weeks later. Two-

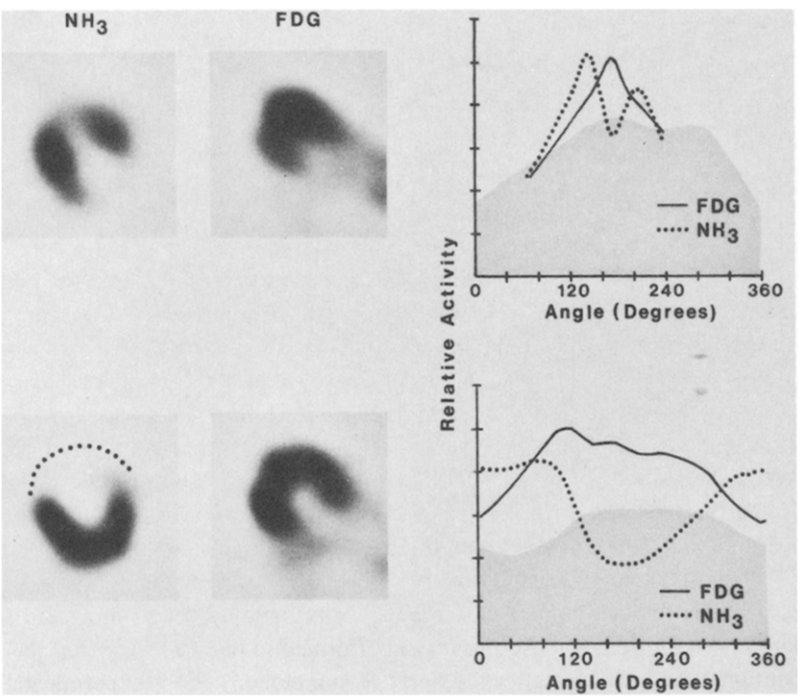


Figure 2. Patient 10. Cross-sectional images after administration of N-13 ammonia (NH_3) and F-18 deoxyglucose (FDG) 40 hours after the onset of symptoms. The two consecutive planes through the left ventricle are displayed. There is decreased N-13 ammonia uptake in the anterior segments of the left ventricle and the F-18 deoxyglucose images reveal increased glucose utilization in these segments with decreased flow. The respective circumferential profiles of relative N-13 and F-18 activity distribution show a clear mismatch of tracer uptake from 80° to 280° (''PET viability''). The **shaded areas** represent values of more than 2 SD below the normal mean.

dimensional echocardiography was performed with the patient in the left lateral decubitus position. Parasternal long-axis and short-axis views and apical four chamber, two chamber and long-axis views were obtained. In one patient, regional function was evaluated with equilibrium radionuclide ventriculography recorded as previously described in the anterior, left anterior oblique and left lateral projections (14).

Regional wall motion was evaluated independently by two observers unaware of the tomographic findings. On two-dimensional echocardiograms and radionuclide ventriculograms, the left ventricle was divided into five segments, each corresponding to a segment defined on the positron emission tomographic images (anterior, septal, apical, lateral and inferoposterior). Regional wall motion was graded visually using the following scoring system: −1 = dyskinesia, 0 = akinesia, 1 = severe hypokinesia, 2 = mild hypokinesia and 3 = normal. Left ventricular ejection fraction was calculated from the four chamber and long-axis views using the area-length method (13). Measurements of left ventricular ejection fraction by this method in our institution correlated with those by left ventriculography in 31 patients with coronary artery disease with a correlation coefficient of 0.89 and standard error of the estimate of 7.9% (unpublished results).

Statistics. Mean values ± SD are given. Data were compared using paired and unpaired Student's *t* tests. A probability value of less than 0.05 was considered significant.

Results

Regional myocardial blood flow and glucose utilization. In the 13 patients, studied an average of 54 ± 12 hours after onset of acute symptoms, positron emission tomography revealed 32 segments with reduced blood flow. N-13 ammonia uptake in these segments averaged 46.9 ± 13.9% of maximal myocardial activity. In the 10 patients with anterior infarction on electrocardiography, blood flow was reduced in the anterior and apical segments of the left ventricle. In the one patient with an inferior infarction, the inferior wall and apex were involved, while in the patient with a posteroinferior infarction, blood flow was decreased in the inferior, apical and lateral segments. Of the two patients with a previous inferior infarction, a segmental blood flow reduction in the inferior wall was observed in only one.

Segments with decreased blood flow revealed two patterns of F-18 deoxyglucose uptake: a) Uptake of tracer was decreased in proportion to blood flow and, consistent with previously established criteria, was defined as "PET infarction" (Fig. 1), or b) tracer uptake was increased relative to blood flow and, consistent with the preceding criteria, was defined as "PET viability" (Fig. 2). The cross-sectional images at the mid-left ventricular level in Figure 1 were obtained in a patient (Case 13) with an anterior infarction 42 hours after the onset of symptoms. The N-13 ammonia images reveal reduced blood flow in the anterior, septal and apical segments of the left ventricle. Glucose utilization in these segments is, as seen on the F-18 deoxyglucose study, concordantly decreased and the pattern resembles "PET infarction." The electrocardiogram recorded on the same day indicated an extensive transmural anteroseptal infarction while the echocardiogram revealed akinesia of the anterior and septal segments and dyskinesia of the apex. Figure 2 shows another patient (Case 10) with an anteroseptal infarction studied 40 hours after onset of symptoms. Again, the N-13 ammonia images reveal diminished blood flow in the anterior and septal segments of the left ventricle accompanied by increased glucose utilization as seen on the F-18 deoxyglucose study. This pattern resembles "PET viability." ST segment elevations were present in the anterior electrocardiographic leads recorded on the day of the positron emission tomographic study; the echocardiogram revealed akinesia of the anterior and anteroseptal segments.

Table 1 summarizes the findings in all 13 patients. Nine patients revealed segments with "PET viability" while the remaining four patients revealed only segments with "PET infarction." In the 32 left ventricular segments with decreased flow, 16 (50%) revealed concordant decreases in glucose utilization; the remaining 16 (50%) were characterized by a discordance between blood flow and glucose utilization. Relative N-13 ammonia uptake averaged 48.2 ± 15.9% of maximal myocardial activity in segments with maintained F-18 deoxyglucose uptake as compared with 46.0 ± 7.4% (p = NS) in segments with concordant decreases of flow and metabolism.

Segmental wall motion. Segmental wall motion was assessed in all patients on the day of the tomographic study and again in 12 patients 6.0 ± 4.6 weeks later. Early after infarction, function was impaired in all segments with decreased myocardial blood flow. The mean wall motion score was 0.46 ± 0.9. In the initial study, wall motion scores were not significantly different between segments with or without F-18 deoxyglucose uptake (0.34 ± 0.84 versus 0.67 ± 0.83). The left ventricular ejection fraction averaged 45.4 ± 16.0% in all patients and was similar in the four patients with only concordant reductions of blood flow and metabolism and in the nine patients with segments of reduced blood flow but maintained glucose utilization (38.5 ± 4.4% versus 44.4 ± 14.9%; p = NS).

Follow-up evaluation of segmental function revealed no change in mean wall motion score in segments with "PET infarction" (acute 0.67 ± 0.83; follow-up 0.69 ± 0.99; p = NS). The left ventricular ejection fraction remained unchanged in the four patients with findings of "PET infarction" only (38.5 ± 4.4% versus 38.8 ± 6.0%). In contrast, wall motion improved in "PET viable" segments from the initial to the follow-up study (0.34 ± 0.84 versus 1.12 ± 1.4; $p < 0.01$). However, functional outcome of individual

Table 1. Summary of Individual Data in 13 Patients

Case	Age (yr)	CK-MB (U/liter)	ECG	PET		WM (Follow-up)	EF(%)		Post Infarct Angina	Coronary Anatomy†
				NH_3	FDG		Early*	Late		
1	41	30	ANT	Ant↓ AP↓	ANT↑ AP↑	ANT↑ AP↑	43	67	+	LAD 95%, RCA 70%, Cx 50%
2	42	26	ANT	SEP↓ AP↓	SEP↑ AP↑	SEP↑ AP↑	60	58	−	LAD 60%
3	75	9	ANT	ANT↓ AP↓	ANT↑ AP↑	ANT→ AP→	59	56	+	—
4	69	179	ANT	ANT↓, SEP↓, AP↓	ANT↑, SEP↑, AP↓	ANT↓, SEP→, AP→	32	31	−	LAD 80%, RCA 50%
5	66	38	ANT, INF	ANT↓ AP↓	ANT↓ AP↓	ANT→ AP→	42	42	−	—
6	83	13	ANT	ANT↓ AP↓	ANT↓ AP↓	—	40	—	−	—
7	48	21	INT, POST	INF↓, LAT↓, AP↓	INF↓, LAT↑, AP↑	INF→, LAT↓, AP↑	38	33	−	RCA 100%, Cx 100%
8	50	30	INF	INF↓ AP↓	INF↑ AP↓	INF↑ AP→	65	50	+	RCA 100%
9	63	24	ANT, INF	AP↓, ANT↓, INF↓	AP↓, ANT↓, INF↓	AP→, ANT→, INF→	32	30	−	RCA 100%, LAD 70%, Cx 80%
10	71	28	ANT	ANT↓, AP↓	ANT↑, AP↑	ANT→, AP→	50	50	+	LAD 80%, Cx 50%
11	81	28	LBBB	ANT↓, LAT↓, AP↓	ANT↑, LAT↓, AP↑	ANT↑, AP→, LAT→	23	31	−	—
12	80	27	ANT	ANT↓, LAT↓, AP↓	ANT↓, LAT↑, AP↓	ANT→, LAT→, AP→	30	44	+	LAD 100%*
13	61	66	ANT	ANT↓, AP↓, SEP↓	ANT↓, AP↓, SEP↓	ANT→, AP↓, SEP→	40	40	−	LAD 100%, Cx 90%, RCA 80%

*Autopsy; †percent stenoses. ANT = anterior; AP = apex; CK-MB = creatine-kinase, MB fraction; ECG = electrocardiogram; EF = ejection fraction; FDG = fluorine-18 deoxyglucose; INF = inferior; LAD = left anterior descending coronary artery; LAT = lateral; LBBB = left bundle branch block; LCx = circumflex artery; NH_3 = nitrogen-13 ammonia; PET = positron emission tomography; POST = posterior; RCA = right coronary artery; SEP = septum; WM = change in wall motion from the initial to follow-up study; + = present; − = absent; ↑ = increased; → = unchanged; ↓ = decreased.

segments was highly variable. Eight of the 16 segments showed improvement of regional function as defined by a change of more than one grade in wall motion score. In the other eight segments, function remained unchanged in six and deteriorated in two (Fig. 3). Consistent with these variable changes in segmental function, the average left ventricular ejection fraction in the nine patients with "PET viable" segments remained unchanged (44.4 ± 14.9% versus 46.7 ± 12.9%).

Five patients had postinfarction angina. All had evidence of F-18 deoxyglucose uptake in the infarcted segment as opposed to patients with "PET infarction" segments only, none of whom experienced chest pain. One patient (Case 9) with "PET infarction" segments developed cardiogenic shock and died during the hospital stay.

Coronary anatomy and positron emission tomographic findings. Eight of the 13 patients had coronary angiography within 10 days of the tomographic study. In the patient who died 11 days after onset of symptoms, the coronary arteries were examined during autopsy.

Coronary angiography revealed single vessel disease in two, double vessel disease in two and triple vessel disease in four patients. The infarct vessel was completely occluded in four patients but was patent although stenotic (79 ± 14% diameter narrowing) in the four remaining patients. Autopsy in the patient who died revealed total occlusion of the proximal left anterior descending artery.

These nine patients had a total of 23 segments with decreased blood flow on positron emission tomography. Thirteen of these segments were in the territory of an occluded coronary artery. Ten segments showed concordant decreases in blood flow and F-18 deoxyglucose uptake on positron emission tomography. Two segments (posteroinferior and lateral wall) with F-18 deoxyglucose uptake had angiographically visible collateral vessels. The remaining segment had persistent F-18 deoxyglucose uptake on positron emission tomography but no angiographic evidence of collateral blood flow. Conversely, 8 of 10 segments with maintained F-18 deoxyglucose uptake were supplied by coronary arteries that were found to be patent at the time of coronary angiography.

Plasma substrate concentrations and medication. Venous plasma glucose, free fatty acids and lactate concentrations at the time of the tomographic study were similar

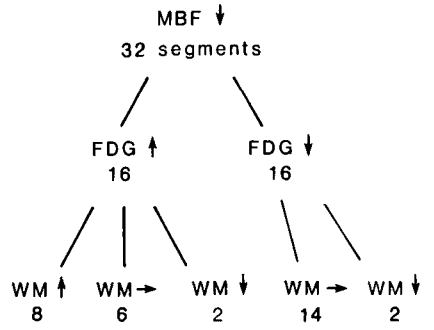


Figure 3. Summary of the positron emission tomographic findings in 13 patients with acute myocardial infarction. Segmental myocardial blood flow (MBF) was determined from N-13 ammonia images and compared with regional glucose utilization (FDG) in 13 left ventricular segments. The change in segmental function (wall motion, WM) was compared with the positron emission tomographic findings. ↑ = icreased; → = no change; ↓ = decreased.

in patients with maintained F-18 deoxyglucose uptake and patients with concordant decreases in blood flow and F-18 deoxyglucose uptake (Table 2).

No patient received positive inotropic drugs or beta-receptor blocking agents at the time of the tomographic study. Three of nine patients with "PET viability" and one of four with "PET infarction" had a lidocaine infusion during the study; six patients with "PET viability" and two of the four patients with "PET infarction" were receiving percutaneously applied nitrate therapy at the time of the study.

Discussion

The results of this study indicate that metabolic imaging with positron emission tomography can identify viable but compromised tissue in patients with acute myocardial infarction. In none of the ventricular segments with concordantly decreased blood flow and glucose utilization early after infarction did function improve. However, segments with decreased blood flow but with evidence of glucose metabolism during the subacute phase of myocardial infarction had a variable functional outcome. This finding suggests a mixture of viable and necrotic cells in the "infarct" area in a considerable number of patients. The relative amount of viable cells may be an important factor in assessing the severity of injury and in the functional outcome of the affected myocardium.

Methodologic considerations. Positron emission tomography was used for noninvasive evaluation of regional myocardial blood flow and exogenous glucose uptake. The poor spatial resolution of the tomograph (1.8 cm FWHM) precluded assessment of transmural tracer distributions and allowed only estimates of averge transmural tracer uptake. Furthermore, as we have shown previously (15), the tissue tracer activity as observed by positron emission tomography depends on myocardial wall thickness (partial volume effect). This causes an underestimation of true tissue activity in segments with wall thinning or severe wall motion abnormalities (16). However, comparison of measurements of blood flow with those of glucose uptake by the same technique is not affected by the partial volume effect. On the other hand, because of these technical limitations, we did not attempt to quantitate regional blood flow or glucose utilization in absolute terms.

The relative distribution of regional myocardial blood flow was evaluated with N-13 ammonia. Previous animal studies (17,18) confirmed the validity of this tracer as a marker of blood flow. In the physiologic flow range, myocardial N-13 ammonia uptake is linearly related to blood flow. Although N-13 ammonia is trapped metabolically in myocardium, metabolic changes over a wide physiologic range as well as acute myocardial ischemia remained without significant effects on the relation between blood flow and regional myocardial N-13 ammonia uptake (18). However, we cannot entirely exclude an impairment of the N-13 ammonia trapping in tissue submitted to prolonged ischemic periods or in postischemic tissue. This would lead to an underestimation of blood flow in the infarcted area. However, previous studies (11) in the chronic dog model after prolonged ischemia and reperfusion showed a close correlation of relative N-13 ammonia uptake and microsphere blood flow.

F-18 deoxyglucose traces transmembranous glucose transport and phosphorylation. Previous animal experiments have validated F-18 deoxyglucose as a tracer of exogenous glucose utilization in normal and ischemic myocardium (19). We determined the relative distribution of F-18 deoxyglucose and N-13 ammonia uptake and compared it with values previously obtained in a control population

Table 2. Plasma Glucose, Fatty Acids and Lactate at the Time of Positron Emission Tomographic Study in All Patients and in Patients With and Without F-18 Deoxyglucose Uptake

	Glucose (mg/100 ml)	FFA (mEq/liter)	Lactate (mg/100 ml)
All (n = 13)	122.6 ± 28.4	0.46 ± .22	11.2 ± 4.9
FDGI (n = 9)	109.9 ± 18.4	0.44 ± .22	10.9 ± 5.7
FDGL (n = 4)	140.4 ± 83.9	0.49 ± .25	11.7 ± 6.7

FDGI and FDGL = with and without F-18 deoxyglucose uptake, respectively; FFA = free fatty acid.

(12). The relative distribution of N-13 ammonia is parallel with that of F-18 deoxyglucose in normal myocardium in humans (12) and animals (11). Infarcted myocardium is identified by a concordant decrease in blood flow and F-18 deoxyglucose uptake, reflecting the low metabolic requirement of scar tissue. Viable but compromised tissue, by contrast, is characterized by a dissociation between blood flow and glucose utilization (11). The relation between blood flow and F-18 deoxyglucose uptake was used to distinguish viable but compromised tissue from necrotic tissue employing previously established criteria (11).

We correlated segmental positron emission tomographic findings with segmental function using two imaging modalities. Potential errors in comparing findings by planar and tomographic techniques were minimized by dividing the left ventricle into five large segments that can be defined independently by each technique. Moreover, the majority of patients in this study had infarction involving the anteroseptal and apical regions of the left ventricle. These regions are readily accessible to study with both positron emission tomography and two-dimensional echocardiography. Although this approach may lower the sensitivity for detecting small metabolic and functional abnormalities, it appeared to increase the specificity of our findings. Segmental function was studied only by noninvasive techniques because their use permitted serial follow-up studies. Although contrast ventriculography may be most accurate, two-dimensional echocardiography and radionuclide ventriculography compare well with contrast ventriculography in assessing regional wall motion (20).

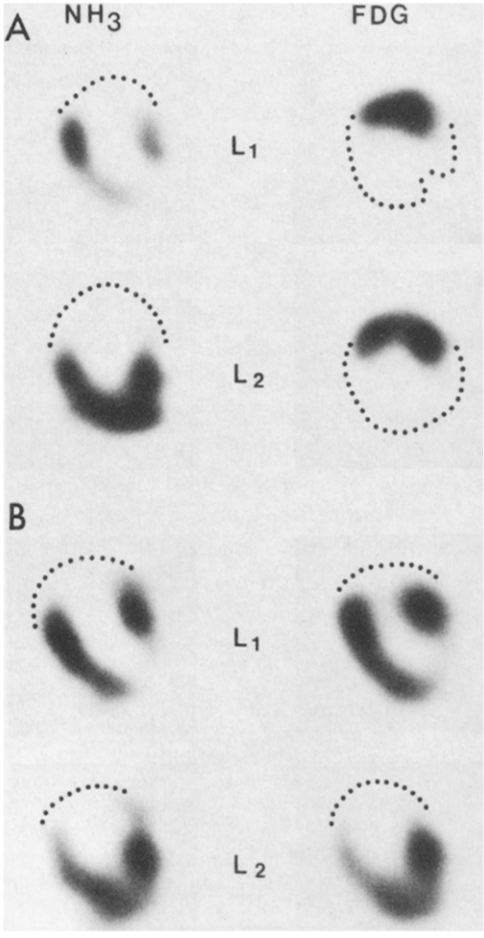
Data interpretation. Myocardial infarction is a complex dynamic pathophysiologic process. Myocardial infarction may be associated with various degrees of collateral blood flow, and spontaneous reperfusion occurs frequently (3,4). These factors favor the presence of a mixture of necrotic and viable, but ischemically injured, myocardium in the affected vascular bed during the subacute phase of myocardial infarction. In our study, about half of the "infarcted" segments with diminished blood flow had residual glucose utilization, indicating the presence of viable tissue. The high incidence of residual viable though compromised tissue during the subacute phase of an infarction suggests spatial and temporal heterogeneity of ischemic injury, with coexistence of myocytes with different degrees of cellular damage. This observation in patients without acute intervention is important in view of strategy and timing of therapeutic interventions.

Increased F-18 deoxyglucose uptake in myocardial segments with decreased blood flow has been previously described in animal and clinical studies (11,12,21,22). In reperfused canine myocardium, regional increases in glucose utilization identified myocardium with little histologic evidence of necrosis and with recovery of function (11). Additional use of C-11 palmitate as a marker of fatty acid metabolism in the same animal model revealed impaired fatty acid oxidation in segments with increased glucose utilization (11). These findings suggest an impairment of fatty acid oxidation and a regional shift in substrate utilization to glucose as the pathophysiologic mechanism for regionally increased F-18 deoxyglucose uptake in ischemically injured myocardium (23).

Tillisch et al. (21) reported in patients undergoing coronary bypass surgery the predictive value of maintained glucose utilization in segments with reduced blood flow reduction for functional recovery after revascularization, supporting the notion that maintained F-18 deoxyglucose uptake identifies viable but compromised tissue that is potentially salvageable.

In these previous studies, restoration of blood flow to

Figure 4. Patient 10. Cross-sectional N-13 ammonia (NH_3) and F-18 deoxyglucose (FDG) images obtained **(A)** acutely 48 hours after the onset of symptoms and **(B)** 6 weeks later. In the acute study, there is a mismatch of F-18 deoxyglucose and N-13 ammonia uptake suggesting viable tissue in the segments with decreased flow. Six weeks after infarction, there is a matching defect of perfusion and flow in the anterior wall consistent with development of necrosis.



compromised tissue accounted for the functional improvement. In contrast, in our study where no intervention was performed, the functional outcome of segments with maintained F-18 deoxyglucose was highly variable. Tissue survival and the degree of functional recovery are likely to depend on residual blood flow to the "infarcted" segment. For example, in two patients (Cases 1 and 2) with almost complete recovery of function, the infarct vessel was patent (95 and 60% residual stenosis, respectively) 10 days after infarction, suggesting spontaneous reperfusion. In all nine patients whose coronary anatomy was assessed, F-18 deoxyglucose uptake was observed in 9 of 13 segments associated with a patent infarct artery. Two additional segments with F-18 deoxyglucose uptake were supplied by collateral vessels observed on arteriography. Conversely, all segments with concordant decreases in blood flow and F-18 deoxyglucose uptake were in the vascular bed of an occluded coronary artery. These observations, although obtained in a relatively small patient sample, emphasize the importance of residual blood flow or recanalization for survival of ischemic tissue. Recent angiographic studies (24) demonstrated significant recovery of segmental function in patients with subtotal occlusion of the infarct vessel early after the onset of symptoms as compared with little if any change in patients with complete occlusion of the infarct artery. Positron emission tomography failed to demonstrate significant differences in residual blood flow between segments with and without F-18 deoxyglucose uptake, and relative N-13 ammonia concentrations were similar in both instances. The low sensitivity of the imaging device used in this study rather than the underlying pathophysiology is likely to account for the absence of a significant difference in tracer tissue concentrations between segments with and without F-18 deoxyglucose uptake.

Despite a significant improvement in the mean wall motion score in "PET viable" segments, there were large interindividual variations. Function improved in eight segments but remained unchanged in six and deteriorated in two. The lack of functional improvement was attributed in one patient (Case 4) to clinical infarct extension, supporting the notion that positron emission tomography did in fact identify viable but jeopardized myocardium. No clinical evidence of reinfarction was noted in the remaining patients with F-18 deoxyglucose uptake but unchanged regional function.

The time course of metabolic and functional recovery after infarction has not been well delineated. The follow-up evaluations of function may have been too early to document recovery. On the other hand, blood flow may have remained depressed over prolonged time periods in the absence of recanalization or development of collateral flow. Regionally increased F-18 deoxyglucose uptake therefore may represent "chronic ischemia" or a regional metabolic adaptation to chronic hypoxia as previously described in patients with postinfarction angina (12).

One patient (Case 10) with increased F-18 deoxyglucose uptake in the anterior wall early after infarction but without subsequent functional recovery was restudied with positron emission tomography 6 weeks after acute infarction (Fig. 4). Blood flow and F-18 deoxyglucose uptake had concordantly decreased, consistent with progression of ischemia to necrosis. There was no clinical evidence for reinfarction between the first and the second study. It is possible that revascularization in this patient could have salvaged the ischemically injured myocardium. Serial positron emission tomographic studies in a larger number of patients will be needed to address this finding to define the time course of myocardial cell death as well as the predictive value of positron emission tomography for salvageable myocardium. Also, quantitative data on blood flow and glucose utilization might allow a more accurate assessment of the degree of blood flow reduction and the amount of residual viable tissue. Both might better predict the long-term outcome of injured myocardium.

Clinical implications. The results of this and earlier studies (12,25,26) demonstrate that positron emission tomography provides unique information in patients with acute myocardial infarction. These studies strongly suggest that the combined evaluation of blood flow and glucose utilization provides a noninvasive means to identify compromised but metabolically active myocardium in ischemic heart disease. Specifically, it allows identification of viable and jeopardized tissue early during evolving myocardial infarction. However, more studies are needed to elucidate the pathophysiologic mechanism of increased F-18 deoxyglucose uptake in ischemically injured tissue.

Evaluation of regional function early after the onset of symptoms failed to distinguish necrotic from injured myocardium, consistent with earlier findings. Wall motion was impaired equally in "PET necrotic" and "PET viable" injured myocardium. Imaging with thallium 201 at rest evaluates the relative distribution of blood flow but remains controversial for defining tissue viability (27). Symptoms of ongoing ischemia occurred in only five of the nine patients with maintained F-18 deoxyglucose uptake, suggesting that ongoing ischemia may frequently occur without symptoms. Therefore, metabolic imaging with positron emission tomography may fill an obvious gap in diagnostic procedures. This noninvasive technique can be performed without significant risk in patients with acute myocardial infarction. It is hoped that accurate quantitation of regional flow and metabolism can be achieved with the new generation of positron emission tomographs (28). Accurate determination of the extent of necrosis and compromised tissue with these newer tomographs will improve and allow establishment of quantitative criteria for blood flow and metabolism which

predict spontaneous tissue recovery. On the basis of such measurements, guidelines for the therapeutic interventions can be developed and patients selected for immediate therapy (29,30).

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